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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Patrick Soon-Shiong

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EXAMINER

ANDERSON, JAMES D

ART UNIT

PAPER NUMBER

1614

DATE MAILED: 08/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/937,840	Applicant(s) SOON-SHIONG ET AL.	
	Examiner James D. Anderson	Art Unit 1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 December 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-5 and 7-47 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 15-17 and 20-25 is/are allowed.
- 6) ☒ Claim(s) 1-5, 7-14, 18, 19 and 26-47 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Applicants' arguments, filed 12/08/2005, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Status of the Claims

Claims 1-5 and 7-47 are currently pending and are the subject of this Office Action. Claims 9, 11 and 14 are currently amended and claims 22-47 are newly presented for examination.

Claim Rejections - 35 USC § 112 – First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Upon further consideration, Claim 8 is rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claim was amended on 8/25/2004 to recite a range from "about 3 weeks to about 3 months." The specification as originally filed does not provide support for a

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lower limit of 3 weeks in the recited range. For example, page 9 of the specification states that, “Exemplary low end points of this sub-therapeutic dose level administration time range include 2 days, 7 days, 14 days (i.e., 2 weeks), and 30 days (i.e., 1 month).” Nowhere does the specification contemplate or describe a low end point of 3 weeks for this time range of administration.

Claims 1-5, 7-14, 18-19 and 26-47 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by “undue experimentation,” the Federal Circuit has stated that:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *PPG v. Guardian*, 75 F.3d 1558, 1564 (Fed. Cir. 1996).¹

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404

¹ As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is “undue”, not “experimentation”.

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wherein, citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

- 1) the quantity of experimentation necessary,
- 2) the amount of direction or guidance provided,
- 3) the presence or absence of working examples,
- 4) the nature of the invention,
- 5) the state of the prior art,
- 6) the relative skill of those in the art,
- 7) the predictability of the art, and
- 8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to methods of treating cancer comprising administering a sub-therapeutic dose level of a pharmacologically active agent. The relative skill of those in the art is high, generally that of an M.D. or Ph.D. That factor is outweighed, however, by the unpredictable nature of the art.

The “predictability or lack thereof” in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. See M.P.E.P. 2164.03

As illustrative of the state of the art, the examiner cites Herben *et al.* (J. Clin. Oncol., 1999, vol. 17, pages 1897-1905).

That article plainly demonstrates that the art of low-dose, continuous chemotherapy is very unpredictable. As discussed in Herben *et al.*, patients with solid tumors received continuous infusions of irinotecan for 14, 17 and 21 consecutive days (Abstract). The starting dose was 175 mg/m^2 (*i.e.* $12.5 \text{ mg/m}^2/\text{day}$). This dose represented 50% of the recommended dose with a schedule of once every 3 weeks (page 1898). As shown in Table 3 (page 1900), gastrointestinal toxicity varied greatly with the different dose levels. Further, the pharmacokinetic parameters of irinotecan also varied with different dose levels and were also very different than the pharmacokinetics of irinotecan when administered “conventionally” (Table 4, page 1901). Because of toxicity, an actual dose-intensity of $125.7 \text{ mg/m}^2/3 \text{ weeks}$ was achieved which is 40% of the dose-intensity obtained with short infusion schedules of irinotecan (page 1903). The authors conclude “The optimal administration schedule of irinotecan in the clinic is still uncertain” (page 1904).

The unpredictability of the present invention is further compounded by the fact that applicants wish to treat cancer with a sub-therapeutic dose of an active agent. By definition, a sub-therapeutic dose will not be effective in treating cancer. If a particular dose is effective in treating cancer then it is, by definition, a therapeutic dose. Munoz *et al.* (The Breast, 2005, vol. 14, pages 466-479), cited for evidentiary purposes only, further highlight this fact. The authors state that a “major handicap” of “metronomic chemotherapy” is the determination of an optimal biologic “low” dose for any given chemotherapy regimen (page 475). Because many new drugs do not have dose-limiting toxicities or express optimal therapeutic activity below a MTD, this “greatly increases the empiricism associated with using these drugs in clinical trials, and hence the probability of obtaining negative results” (page 475).

Yet another example of the unpredictability of low-dose continuous chemotherapy is found in Blumenreich *et al.* (Am. J. Clin. Oncol., 1994, vol. 17, pages 163-165). This reference discloses that etoposide is more active in small cell lung cancer when given over 5 days than as a single injection. The authors wished to examine this concept further by administering a dose of 50 mg by mouth daily. The median duration of therapy was 63 days. Out of 19 patients, 13 patients had progression of disease. No complete or partial responses were observed. The authors conclude, “low-dose continuous oral etoposide is a well-tolerated but ineffective regimen in non-small cell lung cancer” (Abstract).

Long-term continuous infusions of chemotherapeutic agents are well known in the art. For example, Sorensen *et al.* (Acta Oncologica, 1999, vol. 38, pages 1043-1045) describe the long-term continuous infusion of 5-fluorouracil (5-FU) in patients with head and neck cancer (Abstract). The dose administered was 300 mg/m²/day for a maximum of 16 weeks. Even at

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this dose, there was only an objective response rate of 15% in 41 patients. The authors conclude, “[L]ong-term continuous infusion of 5-FU had only modest activity in terms of response rate” (page 1044). Given that a therapeutic dose (in this case, 300 mg/m²/day), continuously administered over 16 weeks, demonstrated only “modest activity” (15% response), it is not clear how administration of a sub-therapeutic dose will treat cancer.

Clearly then, the treatment of cancer with therapeutic doses and “low-doses”, let alone sub-therapeutic doses of an active agent, particularly in humans, is extremely unpredictable.

2. The breadth of the claims

The claims are very broad, reciting the treatment of “cancer” with a “sub-therapeutic dose level” of an “active agent effective against” the cancer being treated. The claims and specification contemplate using any chemotherapeutic agent effective against any particular cancer. Further, the claims are also broad in so far as they recite sub-therapeutic doses of “about 1% up to about 20%” of the “conventionally” administered amount wherein the dose is administered “over an administration time in the range from about 7 days to about 1 year”. Thus, only very general, broad guidance with respect to the administration of sub-therapeutic doses of chemotherapeutic agents is provided by the specification.

3. The amount of direction or guidance provided and the presence or absence of working examples

The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

The specification provides very general direction and guidance for determining the particular administration regimes (dosages, timing, administration routes, etc.) necessary to treat all cancers, particularly in humans, and more particularly using “sub-therapeutic” doses of active agents. No “working examples” are presented in the specification. However, pages 18-19 of the disclosure describe the administration of paclitaxel in the treatment of “cancers responsive to paclitaxel”. Even here, only a broad dose (50-150 mg/m²) is described and this example is prophetic in nature (*i.e.* the efficacy of this administration regimen has not been demonstrated for any cancer). No reasonably specific guidance is provided concerning useful therapeutic protocols for any particular chemotherapeutic or cancer.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed methods could be predictably used as treatments for any and all cancers as inferred in the claims and contemplated by the specification. Further, the skilled artisan would not, *a priori*, have a reasonable expectation that administering a “sub-therapeutic” dose, no matter how long the administration, would be effective in treating cancer. A sub-therapeutic dose is just that, below the therapeutic level. Examiner respectfully submits that, by definition, a sub-therapeutic dose cannot treat cancer. If any particular dose does treat cancer, it is a therapeutic dose.

It is the examiner’s position that the skilled artisan, presented with the instant disclosure, would have to engage in undue experimentation to practice the claimed invention. It is not

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routine experimentation to treat cancer with sub-therapeutic doses of active agents. The art of treating cancer with therapeutic doses of chemotherapeutic agents is itself generally unpredictable. Even in the case of an agent known to treat a particular cancer, the therapeutic dose and administration schedule of that particular agent cannot be readily predicted from *in vitro* or *in vivo* efficacy data.

In the instant case, to treat cancer with sub-therapeutic doses of active agents is even more unpredictable than treating cancer with doses of an agent known to be effective in the treatment of a particular cancer. For example, the pharmacokinetics of a chemotherapeutic agent will vary greatly with different administration schedules. The skilled artisan is faced with the task of determining an administration schedule and dose that effectively treats cancer (*i.e.* is therapeutic) but does not exhibit unwanted and/or intolerable toxicity.

The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff 'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

In the instant case, the art does not *routinely* administer chemotherapeutic drugs in sub-therapeutic doses.

Given the above *Wands* factors analysis, although the specification discloses numerous chemotherapeutics and cancers that can be treated with those chemotherapeutics, and further discloses broad doses (1-20% of “conventionally administered” doses) and administration schedules (“from about 7 days to about 1 year”), the instant specification does not provide the

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skilled artisan with sufficient guidance with respect to the broad nature of the claimed invention.

It would take undue and extremely burdensome experimentation to determine, for each chemotherapeutic and cancer, the “sub-therapeutic” dose that treats the intended cancer without undesirable pharmacokinetics and toxicity. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 112 – Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-5, 7-10, 13-14, 18-19, 37-42 and 46-47 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the administration of a sub-therapeutic dose of a pharmacologically active agent over an administration time of “from about” 7 days to “about” 1 year. This limitation is indefinite because the terms “from” and “about” are mutually exclusive. “From” implies a definite lower limit to the administration time. The court has held that claims reciting “at least about” were invalid for indefiniteness where there was close prior art and there was nothing in the specification, prosecution history, or the prior art to provide any indication as to what range

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of specific activity is covered by the term “about.” *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991). In the instant case, pharmacologically active agents are routinely administered over 96 hours (*i.e.* 4 days). In the broad range instantly claimed, it is not clear that “from about 7 days” would not include 4 days. The specification (page 9) even describes lower end points (*e.g.* 2 days). As was the case in *Amgen v. Chugai*, there is nothing in the specification, prosecution history, or prior art that provide one skilled in the art with any indication as to what range is covered by the term “about” in the instant claims. Claims dependent from Claim 1 are included in this rejection.

Claim 9 recites the limitation “said infirmity” in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claims 13 and 14 recite the limitation “regularly administering”. This limitation is indefinite because it is not clear what administration schedule “regularly administering” is meant to encompass in the instant claims. For example, does regular administration mean continuous administration, once an hour administration or once a day administration? Claims dependent from claims 13 and 14 are included in this rejection.

Allowable Subject Matter

Claims 15-17 and 20-25 are allowed. The prior art does not teach or reasonably suggest unit dosage forms comprising sub-therapeutic dose levels of pharmacologically active agents.

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Conclusion

Claims 1-5, 7-14, 18-19 and 26-47 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James D. Anderson whose telephone number is 571-272-9038.

The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



James D. Anderson
Patent Examiner
AU 1614

August 17, 2006

 8/18/06
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SUPERVISORY PATENT EXAMINER